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10/566,886	02/01/2006	David M. Neville	14028.0295U2	9182

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,886	NEVILLE ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *27-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-39 are pending in this office action.

Election/Restrictions

This application contains claims 27-38 drawn to an invention nonelected with traverse in the reply filed on 2/11/08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

Applicants' amendments to the specification are acknowledged and are sufficient to overcome the objections.

Applicants' arguments regarding the sequence listing in Figure 1 is persuasive and thus the figure is considered to be compliant.

Claim Objections

Claim 39 is objected to because of the following informalities: Claim 39 recites that the *Pichia pastoris* comprises a mutation in the amino acid sequence encoding EF-2. More accurately, the amino acid sequence is EF-2 and therefore it would be remedial to recite--amino acid sequence of EF-2----. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 2/28/08 and restated below. The rejection has been extended to newly added claim 39.**

Claim 10 is drawn to a *Pichia* pastoris comprising a mutation in the amino acid sequence encoding EF-2and claim 39 wherein the mutation prevents ADP ribosylation of EF-2. Therefore, applicants claim a genus of *Pichia* cells comprising mutant EF-2 sequences. The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The specification discloses a single sequence of EF-2 and that is represented by SEQ ID NO: 13. This sequence is used to generate a single species of cells wherein EF-2 is mutated so that the Gly amino acid at position 701 has been changed to an Arg. This mutation results in a

prevention of ADP-ribosylation of EF-2 in other organisms. Hence, applicants demonstrate a single species of cells and that is a cell in which EF-2 (SEQ ID NO:13) has a Gly to Arg mutation at position 701. The court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a sequence requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution • of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Given the large size and diversity of cells and EF2 mutants and the inability to determine which will also have the essential element, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of no species

would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Argument

Applicants' arguments filed have been fully considered but they are not persuasive. EF-2 is elongation factor 2, which is mutated in some embodiments in t the instant method. By recitation of use of an EF-2 with "a mutation", a diverse number of species are contemplated such as substitution, deletions and insertions as well as combinations of these alterations. The number and location of the mutations are not limited nor in claim 10 is the functionality. It is clear from the specification that this mutation must allow production of EF-2 but must affect the ability of EF-2 to be ADP ribosylated. Applicants indicate that each of the His modifications to any number of amino acids constitute with a mutation from Gly to Arg a large genus. However, firstly modification of the His residue in the dipthamide domain is a single species and this species is specifically set forth in the specification as non-desirable. IN fact, the only mutation that is understood to be of value in the method is a Gly to Arg mutation in the dipthamide domain.

> EF-2 is a single polypeptide chain of about 850 amino acids and is composed of two domains. The N-terminal G domain is responsible for binding and hydrolysis of GTP that promotes translation, and the C-terminal R (or dipthamide) domain is thought to interact with the ribosome (Kohno et al., 1986; Perentesis et al., 1992). The dipthamide domain (FIG. 1a) contains a histidine residue in a region of 22 residues that are well conserved in the EF-2 of all eukaryotes. This conserved histidine is specifically modified post-translationally to the derivative, diphthamide, which is the unique target for ADP-ribosylation by DT (Van Ness et al., 1880). In S. cerevisiae, the conserved histidine can be mutated and substitutions with some other 2 amino acids yielded functional EF-2s that were resistant to ADP-ribosylation (Phan et al., 1993; Kimata and Kohno 1994). However, cells with EF-2 mutated at diphthamide grew more slowly than those expressing wild-type EF-2. In CHO cells, a single substitution of arginine for glycine,

which is another well conserved residue located at the 3rd position to the C-terminal side of the diphthamide, also prevented the formation of diphthamide (Kohno & Uchida, 1987; Foley et al., 1992) and resulted in non-ADP-ribosylatable EF-2. This mutation had the same effect on EF-2 of S. cerevisiae (Kimata et al., 1993). In contrast to the mutation at diphthamide, the Gly to Arg mutation in EF-2 did not affect cell growth of CHO and S. cerevisiae (Foley et al., 1992; Kimata and Kohno 1994; Kimata et al., 1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-10, 12, 13, 15-20 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al (US 6,723,536; see entire document) in view of Neville et al (WO 01/87982; see entire document).

Applicants claim a method of expressing an immunotoxin in *Pichia pastoris* comprising growth in enzymatic digest of protein and yeast extract upon which methanol induction is performed at a temperature below 17.5°C.

Neville et al teach expression of proteins in *Pichia pastoris* wherein growth in is enzymatic digest of protein and yeast extract which methanol induction. Growth media comprises 4% glycerol, *about* 2% yeast extract, 2% enzymatic digest of protein, 1.34% yeast nitrogen base with ammonium sulfate and without amino acids, .43% PTM1 solution, wherein growth occurs at pH 3.5, and 0.01% antifoaming agent. Dissolved oxygen is about 40% (see figure 41). Methanol induction is performed at pH 7.0 wherein the agitation is 800 rpm (about

400 rpm) see page 159. Casamino acids and yeast extract serve as a source of amino acids and PMSF for at least 2 hours (it maintained expression level for 11 hours; see page 160, ¶ 2). Neville teach us of a mutant *Pichia pastoris* cell that comprises a mutation in the EF2 gene and is used for expression of A-dmDT390-bisFV(UCHT1) (see figure 20 and page 138, ¶ 4, page 55, line 1-5).

Neville et al do not teach that the temperature is below about 17.5°C.

Madsen et al teach methods of producing recombinant proteins wherein *Pichia* cells are grown in media comprising enzymatic digestion of protein and yeast extract (see col 7-8). Methanol induction was performed wherein the induction was performed at less than about 17.5°C (see col 7, line 35-44), which range encompasses 15°C. Glycerol containing media is fed to the glycerol containing cells and dissolved oxygen is 30% (see col 8, batch glycerol phase).

As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte* Smith --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In the instant case, the combination of Neville et al and Madsen et al demonstrates an attempt to use known techniques to improve similar methods of protein expression using *Pichia* based upon skill that was available at the time of filing with well-established methods. In the instant case, there are multiple overlapping methods used to cultivate *Pichia* for protein expression. Madsen et al is directed to teaching methods of methanol induction in which the temperature is low. Neville et al teach methods of expressing *diphtheria toxin* using *Pichia* using methanol induction. It would have been obvious to one skilled in the art to make a substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the

invention. Furthermore, the claims would have been obvious because a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 2, 4, 11, 14, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al (US 6,723,536; see entire document) in view of Neville et al (WO 01/87982; see entire document) as applied to claims 1, 3, 5-10, 12, 13, 15-20 and 22-25 above, and further in view of Magota et al (6,171,828; see entire document) and McGrew et al (Gene, 1997, Vol 187(2), pages 193-200; see entire document) and Chang et al (US 6,992,172; see entire document).

The teachings of Neville et al in view of Madsen et al are as above, except neither teaches specifically that methanol induction occurs by 1) limited methanol feed of 0.5-0.75 ml/min/10L or 2) a glycerol:methanol feed wherein the ratio of glycerol to methanol is 4:1. Nor do any of the previously cited references teach use of soy digest of protein.

Magota teaches methanol induction in which methanol is fed into the culture at a rate of between 1.5 ml/L/hr and 4.7 ml/L/hr (see figure 4) which correlates for a 10L culture to 0.25 to 0.78 ml/min.

McGrew et al teach that a glycerol:methanol feed can be used to successfully induce heterologous protein expression in *Pichia* cells wherein the ratio of glycerol to methanol is 4:1 (see table).

Chang et al teach that enhanced expression is accomplished by use of soytone which is a digest of soy protein (see e.g. col 59, line 29-55).

It would have been obvious to one skilled in the art to make a substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant rejection, Magota et al, McGrew et al and Chang et al demonstrate that methods involving expression of proteins from *Pichia* are known and recognized to use methanol induction wherein either 1) limited methanol feed of 0.5-0.75 ml/min/10L or 2) a glycerol:methanol feed wherein the ratio of glycerol to methanol is 4:1. As well, Chang et al teach that soytone in the media resulted in a plant-derived (rather than animal-derived) media component that lead to increased expression of recombinant protein (see e.g. 59, line 29-55). Furthermore, the claims would have been obvious because the techniques of methanol induction by 1) limited methanol feed of 0.5-0.75 ml/min/10L or 2) a glycerol:methanol feed wherein the ratio of glycerol to methanol is 4:1 as well as use of soytone were recognized as part of the ordinary capabilities of one skilled in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants' arguments filed 5/28/08 have been fully considered but they are not persuasive. In this case, Madsen et al teach that methanol induction commences at a temperature of below 20°C and based on the lack of clear meaning of the phrase "about", one of skill in the

art would not recognize a significant difference between 20°C and about 17.5°C. The MPEP teaches, (2111.02), " The specification should also be relied on for more than just explicit lexicography or clear disavowal of claim scope to determine the meaning of a claim term when applicant acts as his or her own lexicographer; the meaning of a particular claim term may be defined by implication, that is, according to the usage of the term in >the< context in the specification. See Phillips v. AWH Corp., *>415 F.3d 1303<, 75 USPQ2d 1321 (Fed. Cir. 2005) (en banc); and Vitronics Corp. v. Conceptronic Inc., 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996). Compare Merck & Co., Inc., v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1370, 73

USPQ2d 1641, 1646 (Fed. Cir. 2005), where the court held that patentee failed to redefine the ordinary meaning of "about" to mean "exactly" in clear enough terms to justify the counterintuitive definition of "about." ("When a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, he must clearly express that intent in the written description.")."

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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